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Surgery for patients with “lower grade” glioma: putting assumptions, beliefs and convictions into perspective

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For decades neuro-oncology meetings have benefited from controversial, sometimes heated and emotional debates on the role of surgery for what has traditionally been falsely designated “low grade” glioma; falsely since “low grade” glioma evokes false expectations for often young patients and their caregivers confronted with a disease with a median survival around 7-8 years.

Advocates of either radical surgery for almost everybody or surgery for almost nobody have repeatedly stated their concerns that randomized clinical trials in that situation would be unethical: what more evidence would we need to define a clinical trial as ethical if there is so little agreement among the “experts”?

Yet, in the absence of randomized data to address this question and in the absence even of efforts to do obtain such data, the Norwegian study, facilitated by a small population living in a big country with apparently little patient mobility at the time that the study was conducted, is one of the best estimates of the potential impact of early efforts at resection in patients with World Health Organization (WHO) grade II gliomas. In 2012, Jakola and colleagues reported their first comparison of two management strategies for patients with these tumors in two regions of Norway: one hospital (A) preferred a wait and scan strategy after biopsy whereas another hospital (B) favored early resections. In the initial report [1], median survival was 5.9 years for patients initially managed in hospital A whereas it was not reached in hospital B.

Estimates for 5-year survival were 60% versus 74%. Multivariable analyses determined the relative hazard ratio for death to be 1.8 when a patient was treated in hospital A as opposed to hospital B.

In the present update [2], long-term survival data are reported: median overall survival was 5.8 years in hospital A as opposed to 14.4 years in hospital B. Importantly, the authors undertook a recommendable effort to provide a molecular marker-based stratification of their cohorts according to the new WHO classification and determined that the potential impact of efforts at early resection remained after adjustment for molecular phenotype: IDH mutant 1p/19q codeleted versus IDH mutant versus IDH wild-type.

Admittedly, the study has several limitations which include, amongst others, that with a median age of 44-45 years in both arms, at least half of the patients were in an "elder" age group where most centers would probably not advocate a wait-and-scan strategy in the first place, moreover, the molecular data suffer from the limitation that these data were not assessed centrally or according to the same methodology.

The extensive literature on the role of surgery in gliomas suffers from many assumptions, overinterpretations and misconceptions, and many publications are overtly driven by bias [3,4]: for instance, numerous publications claim *effect* or *impact* of surgery for gliomas although non-randomized retrospective cohort studies [5-7] can detect associations with outcome at best, but by definition can never demonstrate effect or impact (although the Norwegian data set comes relatively close to that).

Similar considerations apply to the discussion of surgery for WHO grade IV gliomas (glioblastomas). There is an almost bizarre discussion on estimating the extent of resection in precise percentages [8] while logics tell us that residual tumor volume – rather than extent of resection - should be in the focus [9], irrespective how big the

tumor, glioma of either WHO grade II, III or IV, was on preoperative scans. A 90% resection of a 100 mm^3 tumor still leaves a lesion of double size relative to a 50% resection of a 10 mm^3 tumor.

Given the plethora of publications that have not advanced the controversy in this area to a relevant extent, the Norwegian data likely provides (one of) the strongest pieces of evidence to support a role for early surgical interventions in patients with so called “low grade” gliomas. Importantly, it indicates a role of surgery across the three major molecular phenotypes of these tumors defined by the 2016 WHO classification. This does not contradict, but rather complements the recent research focus on whether and how molecular markers determine resectability of gliomas [10].

Where do we go from here? Will the present study [1,2] remain to be the best evidence to support a role for surgery in WHO grade glioma? While extent and also timing of surgery remain central topics in clinical research on these tumors, the WHO classification has started to dissect this group of tumors into smaller entities, and new questions arise, notably on targeted systemic treatments e.g. focusing on mutant isocitrate dehydrogenase either as a pharmacological or an immunotherapeutic target. In that emerging landscape of clinical trials, it is increasingly unlikely that the question of surgery will ever be answered in a much more conclusive way than here [1,2].

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